

REMARKS

Claims 11-14 are pending in this application after entry of this paper. Claims 1-10 have been canceled without prejudice. Applicants reserve the right to prosecute subject matter of the canceled claims in one or more continuation, continuation-in-part, or divisional applications. Claims 11-14 have been added. No new matter has been introduced with these amendments. Applicants respectfully request reconsideration and withdrawal of the claim rejections in view of the following amendments and remarks.

Support for New Claims

Support for new claims 11 and 12 can be found throughout the instant specification, drawings, and claims as filed. For example: support for the preamble can be found in previously presented claim 1 and on page 9 (last paragraph); support for step (a) can be found in previously presented claim 1, and on page 8 (last paragraph), page 9 (last paragraph), and page 12 (paragraph 1); support for step (b) can be found in previously presented claim 1 and on page 12 (paragraph 1); support for step (c) can be found in previously presented claim 1 and on page 11 (paragraph 2) and page 12 (paragraph 1); support for step (d) can be found in previously presented claim 1 and on page 7 (paragraphs 2 – 4), page 9 (last paragraph), page 10 (last paragraph), and page 11 (last paragraph) – page 12 (paragraph 2), and in Figures 1-4; support for step (e) can be found on page 7 (paragraphs 2 – 4), page 11 (paragraph 2) - page 12 (paragraph 2), and in Figures 1-4.

Support for claims 13 and 14 can be found throughout the instant specification, drawings, and claims as published. For example: support for the preamble can be

found in previously presented claim 1 and on page 10 (first paragraph); support for step (a) can be found in previously presented claim 1, and on page 8 (last paragraph), page 9 (last paragraph), and page 12 (paragraph 1); support for step (b) can be found in previously presented claim 1 and on page 12 (paragraph 1); support for step (c) can be found in previously presented claim 1 and on page 11 (paragraph 2) and page 12 (paragraph 1); support for step (d) can be found in previously presented claim 1 and on page 7 (paragraphs 2 – 4), page 9 (last paragraph), page 10 (last paragraph), and page 11 (last paragraph) – page 12 (paragraph 2), and in Figures 1-4; support for step (e) can be found on page 10 (first paragraph) and page 12 (paragraph 2).

Amendments to the Specification

No new matter is introduced with this amendment and support can be found throughout the instant application and claims as published. This amendment is submitted in order to clarify the originally submitted Japanese to English translation of the specification.

Response to 35 U.S.C. §101

Claims 1 and 10 have been rejected for allegedly being directed to non-statutory subject matter. Specifically, claims 1 and 10 have been rejected for allegedly encompassing a method of monitoring expression of a gene in a human having a PHM4 gene knocked out. Applicants respectfully disagree with the Examiner's contention and assert that the PHM4 gene knockout was specifically in reference to the yeast host.

However, in order to expedite prosecution and solely for the allowance of the instant application, applicants have cancelled claims 1 and 10 and have added new claims 11-14. Claims 11 and 13 encompass “an animal host cell” and claims 12 and 14 encompass “a yeast host cell whose PHM4 gene is knocked out.” Applicants believe that these amendments address the Examiner’s concerns with regard to this non-statutory subject matter rejection. Applicants, therefore, respectfully request reconsideration and withdrawal of the 35 U.S.C. §101 rejection to these claims in view of the above mentioned claim amendments.

Response to 35 U.S.C. §112, First Paragraph Rejection (written description)

Claims 1 and 10 have been rejected under 35 U.S.C. §112, First Paragraph Rejection for allegedly failing to comply with the written description requirement. Applicants respectfully disagree with the Examiner’s contentions.

Specifically, the Examiner contends that the phrase “animal or a yeast whose PHM4 gene is knocked out” cannot be found in the specification as filed. Applicants respectfully disagree with the Examiner’s contention and again assert that the PHM4 gene knockout is in reference to the yeast host and not the animal host. However, for clarity and in order to expedite prosecution and solely for the allowance of the instant application, applicants have cancelled claims 1 and 10 and have added new claims 11-14. Claims 11 and 13 encompass “an animal host cell” and claims 12 and 14 encompass “a yeast host cell whose PHM4 gene is knocked out.” Applicants believe that these amendments address the Examiner’s concerns and make it clear that the PHM4 knockout is only in reference to the yeast host cell. Support for the yeast host

having its PHM4 gene knocked out can be found throughout the specification as filed, for example on page 4 (last paragraph), page 7 (paragraphs 2 and 4), page 11 (paragraph 2), page 12 (paragraph 2) and Figures 1, 3, and 4 of the application as filed.

Additionally, the Examiner contends that the phrase “target gene” is allegedly new matter. The Examiner further contends that paragraph 18 of the published application (page 9; paragraph 2 of the filed application) is limited to target genes of transcription factors (Office Action, page 3). Applicants disagree with the Examiner’s contention and respectfully direct the Examiner’s attention again to page 9 (paragraph 2) of the application as filed, which clearly states: “As for which genes may be studied by the method of monitoring described by the present invention, there are no particular restrictions” (emphasis added). This paragraph further provides a non-exhaustive list of target genes which may be monitored by the instant invention. One skilled in the art would understand that this is an exemplary list of genes which may be monitored and would not construe this as a limited set of genes. Furthermore, one skilled in the art would recognize and appreciate that the claimed invention is not restricted to the listed target genes and could be utilized for any target gene. The instant specification does not imply or suggest that the claimed invention should only be limited to transcription factor genes. Therefore, applicants assert that the phrase “target gene” is not new matter as it is adequately described and exemplified in the instant specification and one skilled in the art would understand the meaning of this term.

Additionally, the Examiner contends that the step of “preparing a plasmid in which a polyphosphate kinase (PPK) gene is connected in frame and downstream of the target gene” is allegedly new matter (Office Action, page 4). Applicants respectfully

disagree with the Examiner's contention. Applicants once again respectfully direct the Examiner to page 8 (first paragraph) of the application as filed, which states: "As for the polyphosphate sythetases used, there is no particular restriction as long as the synthetases can generate polyphosphate intracellularly. PPK (polyphosphate kinase)... other than PHM of the aforementioned *Saccharomyces cerevisiae* can be used" (emphasis added). Additionally, page 9 (last paragraph) states: "PPK can synthesize polyphosphate from ATP in a single step" (emphasis added). Based on this, one skilled in the art would recognize that PPK is a synthetase (*i.e.*, an enzyme that can catalyse the joining of two phosphate molecules), despite the fact that the word "synthetase" is not part of its name. Hence, one skilled in the art would understand that PPK could be used with the instant invention and that either gene could be connected in frame and downstream of the target gene, based on the description in the specification.

Additionally, the Examiner contends that the step of "introducing the plasmid into a host cell, a tissue, or an organ" in step 2 is allegedly new matter (Office Action, page 4). Applicants respectfully disagree with the Examiner's contention, however, in order to expedite prosecution and solely for the allowance of the instant application, applicants have cancelled claims 1 and 10 and have added new claims 11-14. Claims 11 and 13 encompass "an animal host cell" (emphasis added) and claims 12 and 14 encompass "a yeast host cell whose PHM4 gene is knocked out" (emphasis added) and all claims contain the step of introducing the plasmid into the host cell. Applicants respectfully direct the Examiner's attention to page 12 (paragraph 1) of the instant application which supports the step where the plasmid is introduced into a host cell, and also supports the step of culturing the selected transformant. Furthermore, applicants

assert that techniques for introducing plasmids into yeast and animal cells were well established at the time the application was filed (See, A. Flint, et al. "Co-transfected SV40 origin of replication activates expression from SV40 promoterless constructs." *Biotechniques*. 1999 Oct; 27(4):728-32 and A. Hinnen, et al, "Transformation of yeast." *Proc Natl Acad Sci U S A*. 1978 Apr; 75(4):1929-33; abstracts submitted herewith). Therefore, one skilled in the art would understand that this step is required and would also know how to perform this step by a number of available techniques.

Additionally, the Examiner contends that the step of "inducing expression of the PPK gene" in step 3 is allegedly new matter (Office Action, page 4). Applicants respectfully disagree with the Examiner's contention. Applicants respectfully direct the Examiner's attention to page 12 (paragraph 1) of the instant application which describes the plasmid GAL1 promoter, and the growth conditions for inducing expression, which include, for example, growing cells in media containing galactose. One skilled in the art would understand that in order to induce gene transcription of the plasmid, the GAL1 promoter needs to be activated. Applicants respectfully direct the Examiner to Lohr D, et al. ("Transcriptional regulation in the yeast GAL gene family: a complex genetic network." *FASEB J*. 1995 Jun; 9(9):777-87; submitted herewith), which shows that activation of the GAL1 promoter with galactose was known in the art at the time the instant application was filed.

Additionally, the Examiner contends that the step of quantifying in step 4 is allegedly new matter (Office Action, page 4). Applicants respectfully disagree with the Examiner's contention. As an initial matter, applicants believe that the new claims, compared to the previously presented claims, address the Examiner's concerns

regarding this rejection. Furthermore, applicants respectfully direct the Examiner's attention to page 8 (first paragraph), page 10 (paragraphs 1-2), page 11 (paragraph 2) – page 12 (paragraph 2), and Figures 1-4 of the instant specification which describe the step of quantifying the accumulation of polyphosphate having a strand length equal to or less than 50 mer in the selected transformant by one-dimensional ^{31}P -NMR and/or ^1H -NMR imaging as described in the instant claims. Therefore, applicants believe that the new claims and disclosure in the instant specification address the Examiner's concerns.

Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, First Paragraph rejections to the pending claims in view of the above mentioned claim amendments and remarks.

Response to 35 U.S.C. §112, First Paragraph (enablement)

The Examiner takes the position that enablement cannot be addressed at this time (Office Action, page 5). Applicants believe that the above-mentioned amendments and remarks address the Examiner's concerns and believe that the claims are fully enabled as to how one skilled in the art could make and use the claimed invention by the disclosure in the specification. Therefore, applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112 (enablement) rejection to the claims.

Response to 35 U.S.C. §112, Second Paragraph (indefiniteness)

Claims 1 and 10 have been rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite for failing to provide antecedent basis for the phrase "the

host.” Applicants have cancelled claims 1 and 10 and have added new claims 11-14. The new claims have replaced the word “the” with “a” / “an.” Applicants believe that this amendment addresses the Examiner’s concerns with regard to this rejection.

Additionally, the Examiner contends that the structure of the plasmid does not correlate to a knockout of PHM4 (Office Action, page 5). Applicants respectfully disagree with this contention. Applicants assert that the plasmid correlates to a knockout of PHM4 by replenishing the polyphosphate synthesizing enzyme (*i.e.*, PPK or PHM4) which is deficient in the knockout host. As previously described, the PHM4 knockout relates to the yeast host (now presented in claims 12 and 14). Moreover, the disclosure on page 5, lines 9-11, of the instant specification states that: “[a]ccumulation of polyphosphate cannot be seen at all in ... [the] *phm4Δ*line.” Thus, according to the instant invention, a yeast host cell which has its PHM4 gene knocked out can only accumulate a detectable amount of polyphosphate if it expressed a polyphosphate synthesizing enzyme (*i.e.*, PPK or PHM4) which was expressed from “a plasmid encoding PPK [or PHM4] operably linked downstream of a target gene” (Office Action, page 5) that was introduced into the cell.

Additionally, the Examiner contends that it is unclear how the “host” in the preamble relates to the “host cell, a tissue or an organ” in the body of the claim. Applicants respectfully disagree with the Examiner’s contention; however, in order to expedite prosecution and solely for the allowance of the instant application, applicants have cancelled claims 1 and 10 and have added claims 11-14. The new claims now refer to a “host cell” in both the preamble and the body of the claim. Applicants believe that this amendment addresses the Examiner’s concern relating to this rejection.

Additionally, the Examiner contends that claims 1 and 10 are indefinite because the phrase “quantifying accumulation of polyphosphate having a strand length equal to or less than 50 mer in the mean value and produced by the transformant after the expression has been induced” (Office Action, page 6). Applicants respectfully disagree with the Examiner’s contention; however, in order to expedite prosecution and solely for the purpose of allowance of the instant application, applicants have cancelled claims 1 and 10 and have added claims 11-14. The previously presented phrase has been replaced with “quantifying accumulation of polyphosphate having a strand length equal to or less than 50 mer by one-dimensional ^{31}P -NMR and/or ^1H -NMR imaging.” Applicants believe that this amendment addresses the Examiner’s concerns by setting forth the metes and bounds of the polyphosphates being quantified.

Additionally, the Examiner contends that “it cannot be determined how to distinguish PPK made by the transformant after expression has been induced from PPK made by the transformant before expression is induced” (Office Action, page 6). Applicants believe that there is a misunderstanding, as the instant application does not suggest or claim the quantification of PPK. The instant application is concerned with quantifying polyphosphates. If, in fact, the Examiner meant polyphosphates (as opposed to PPK), then the applicants assert that one skilled in the art would clearly understand how to distinguish polyphosphates made by the transformant before/after the induction of PPK, namely, the level of polyphosphates before expression would be zero (0) and the level after expression of PPK would be greater than zero (0). In other words, polyphosphates will not be produced until after a synthesizing enzyme (*i.e.*, PPK or PHM4) is expressed.

Finally, the Examiner contends that “[i]t cannot be determined how to distinguish polyphosphates having a mean value strand length equal [to] or less than 50 mer from those that do not” (Office Action, page 6). Applicants respectfully disagree with the Examiner’s contention. However, in order to expedite prosecution and solely for the purpose of allowance of the instant application, applicants have amended the specification on page 8 (last paragraph) of the instant specification, to clarify the Japanese to English translation. Applicants assert that no new matter has been introduced by this amendment and support can be found throughout the instant application as filed. Furthermore, applicants have cancelled claims 1 and 10 and have added new claims 11-14. In new claims 11-14, the claim language in the fourth step (*i.e.*, step (d)) correlates with the amendment to the specification to page 8 (last paragraph). Applicants assert that one skilled in the art would understand the amended sentence in the specification to have the same meaning as the one which was originally presented. Applicants believe that the amendment to the specification and the language in the new claims address the Examiner’s concerns.

Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, Second Paragraph rejection to the claims in view of the above mentioned amendments and remarks.

Response to 35 U.S.C. §102(b)

Applicants acknowledge that the 35 U.S.C. §102(b) rejections based on Sharfstein and Voorthuysen have been withdrawn.

CONCLUSION

Based on the foregoing amendments and remarks, the applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

AUTHORIZATION

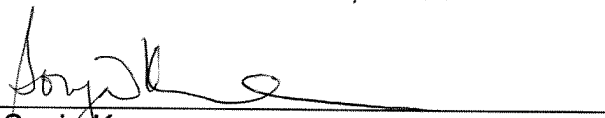
The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **13-4500**, Order No. 4439-4023.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **13-4500**, Order No. 4439-4023.

Respectfully submitted,
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By: _____


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